# PDA-BASED GEO-TAGGED MALARIA INDICATOR SURVEY SOFTWARE AND AN AGENT-BASED MODEL OF THE *ANOPHELES GAMBIAE* MOSQUITO LIFE CYCLE

A Dissertation Proposal

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by

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# CHAPTER 3

# THE AGENT-BASED MODEL (AGiLESim) OF THE *ANOPHELES GAMBIAE* MOSQUITO LIFE CYCLE

## 3.1 Introduction

In this proposal, we will describe an agent-based model for simulating the *Anopheles gambiae* mosquito life cycle by tracking *Anopheles'* eight distinct life states and the transitions among these states. The purpose of our study is to build a core model which reasonably presents the biology and behavior of *Anopheles* mosquitoes, and provides the basic framework for further research, such as exploring the impact of genetic mutation in *Anopheles* mosquitoes on the current malaria control interventions.

## 3.2 Background

### 3.2.1 Significance of Modeling the Life Cycle of *Anopheles Gambiae* Mosquitoes

Malaria is a mosquito-borne infectious disease. Of the approximately 430 known species of *Anopheles*, this disease is transmitted among humans by only 30-50 species of adult females [61]. There are two ways to decrease malaria transmission from the perspective of mosquitoes. One is to reduce the population of mosquitoes. Another is to change the population age structure and shorten adult

mosquito longevity. Some control efforts such as Indoor Residual Spraying (IRS) actually use the later method to interrupt malaria spread.

Because of its critical role in the malaria transmission, understanding and modeling its population dynamics and behavior can help understand how malaria can be endemic in an area, and assist in designing cost-effective malaria control strategies to restrict malaria transmission to a lower level.

### 3.2.2 Equation-based Models (EBMs) vs. Agent-based Models (ABMs)

EBMs identify system variables and are a set of equations that express the relationships among these measurable variables. These equations may be algebraic or more complex differential functions, capturing the variability of the system over time and space.

Agent-based models consist of heterogeneous micro-entities, referred to as "agents". In [26] and [27], the authors summarize the characteristics of an agent as follows:

1. An agent is a discrete entity with a set of attributes and behaviorial rules that make the agent be autonomous.

2. An agent is always living in an environment where it interacts with other agents.

3. An agent has the ability to learn and adapt its behaviors over time. So an agent might have some rules that modify its existing behaviorial rules.

These behavior encapsulated agents make up the whole simulation system.

EBMs and ABMs also share some common characteristics. To simulate a system, both approaches construct a conceptual model. And then they program and

execute it on a computer. In both models, individuals and measurable characteristics are recognized. In addition, ABMs can have equations in them too. For example, in [31], the larval density-dependent mortality was approximated by a function having three independent variables.

The two ways in which equation-based models and agent-based models essentially differ were well discussed in [25]. One is the relationships among objects in their models. EBM starts with equations that state relationships among system variables. The evolution of the variables through time is attained by evaluating these equations. ABM begins with individual behavior rules based on which agents interact to each other. In ABM, direct relationships among system variables are not an input of the simulation, but an output. Another fundamental difference is the level they focus on. EBM focuses its attention on making use of system-level variables. On the contrary, ABM defines agent behaviorial rules in terms of individual-level information. In other words, the system-level variables are not explicitly used to drive the dynamics in ABM.

### 3.2.3 History of Modeling Malaria Epidemiology

In the history of mathematical modeling malaria epidemiology, the traditional differential or difference equation-based models [17, 18, 19, 20, 21, 22, 23, 24] played an very important role. In the early 1910's, Ross first generalized a mathematical epidemic model for malaria as a host-vector disease in 1911 [17]. He also discovered the existence of malaria transmission thresholds that only if the number of *Anopheles* per head of population exceeds a certain figure, can malaria break out. In the 1950's, as early successes with DDT (dichlorodiphenyltrichloroethane) used for a global campaign of malaria eradication, Macdonald developed the Ross's

work further. His model [18] implied that the mortality of adult female vectors is the most critical element in the malaria life cycle, and he also mathematically concluded the impact of reducing mosquito longevity on malaria transmission. In the Macdonald's model, the concept and mathematical expression of basic reproductive number ($R_0$), the mean number of secondary cases a typical single infected case will cause in a population, was first presented in malaria epidemiology. This metric helps determine whether malaria will spread through a population or will be extinct in the long run. But his model ignored the influence of human population dynamics such as human immunity on transmission. Later, in the 1970's, immunity and superinfection of the human population were first presented by the Dietz's mathematical model [19]. This model defined the immunity of the human population as a function of the dynamics of the vector population, and specified a critical vectorial capacity, below which malaria cannot be maintained at an endemic level. More recently, a few individual-based simulation models of malaria epidemiology have been presented [7, 8, 9, 10]. For example, a discrete-event model of malaria epidemiology [8] defined interactions among individual humans and mosquitoes as stochastic events governed by biological rules. It also represented the development of *Plasmodium falciparum* in these individuals. The immunity of human individual was also incorporated in this model. But they largely ignored mosquito population dynamics. For another instance, in [10], an individual-based model of *Plasmodium falciparum* malaria transmission was presented. This model tracked the dynamics of human hosts and adult female mosquitoes individually and the human-vector contracts, and also incorporated human immunity as a function of human exposure history. They used this model to evaluate the effect of two kinds of malaria control programs: reducing human-vector contact rates and implement-

ing malaria case detection and drug treatment.

These models helped researchers better understand malaria dynamics, more wisely analyze collected field data and make more realizable predictions about when, where and how malaria may break out and spread. What the mathematical models had in common is that they investigated the relationship among hosts, vectors and malaria parasites at the population level, assuming the hosts and vectors in their models were identical. And they also have a high requirement for complex mathematics. However, when simulating malaria epidemiology, agent-based models allow us to take considerable individual variability of parasites, hosts and vectors into account, and investigate how macroscale properties such as Entomological Inoculation Rate (EIR) emerge from microscale interactions and adaptive behavior of heterogeneous individuals. In these models, randomness in decision making and various parameters from statistical distributions can be easily incorporated.

### 3.2.4 Advances in Computing Power

Now, hardware capability is no longer a bottleneck that impedes progress toward large-scale data-intensive simulations. As the development of both hardware and software technology, such as multi-core processors [57], faster but cheaper memories, larger capacity but lower cost hard disks, high speed Gigabit networks and powerful distributed computing clusters and grids, it is easier and possible to build large-scale compute-intensive agent-based simulations in a variety of areas [7, 8, 9, 10].

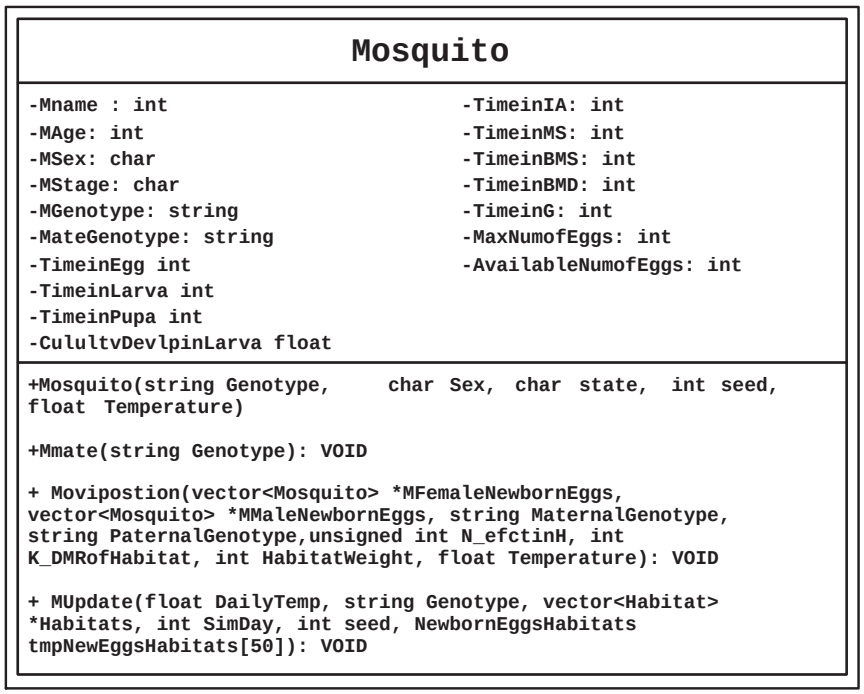


Figure 3.1. The Mosquito Class Diagram.

## 3.3 Model Overview

### 3.3.1 Agents in the Model

There are two kinds of agents in AGiLESim: mosquito and habitat.

Each mosquito agent is distinguished by a number of elementary characteristics: age, sex, genotype, stage and so on. It also has some specific behaviors such as mating and state updating. The mosquito class diagram is shown in Fig. 3.1.

Each habitat agent is characterized by the attributes such ecological factors as carrying capacity, the numbers of eggs, larvae and pupae. It also employs the adding, killing and updating functions to maintain the development time and daily mortalities of mosquito eggs, larvae and pupae within it. At present, we have

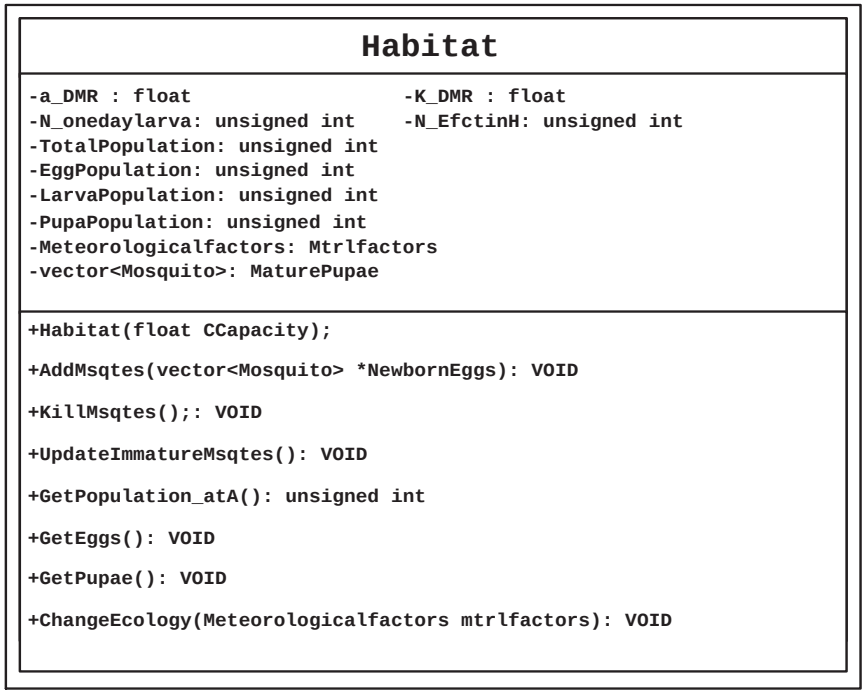


Figure 3.2. The Habitat Class Diagram.

not taken spacial properties into account. So there is no geographical difference among habitats. Fig. 3.2 is the habitat class diagram.

### 3.3.2 Phases and Processes in the *Anopheles* mosquito life cycle

In our model, the *Anopheles* mosquito life cycle shown in Fig. 3.3 has two distinct phases: aquatic and adult. In the aquatic phase, there are three sub-stages: egg ($\boldsymbol{e}$), larva ($\boldsymbol{l}$) and pupa ($\boldsymbol{p}$). We also subdivide the adult phase into five sub-stages, which are ImmatureAdult ($\boldsymbol{IA}$), MateSeeking ($\boldsymbol{MS}$), BloodmealSeeking ($\boldsymbol{BMS}$), BloodmealDigesting ($\boldsymbol{BMD}$) and Gravid ($\boldsymbol{G}$). Of these five adult stages, only ($\boldsymbol{IA}$) and ($\boldsymbol{BMD}$) are temperature-dependent. And the development time in the three aquatic sub-stages also rely on daily temperature.

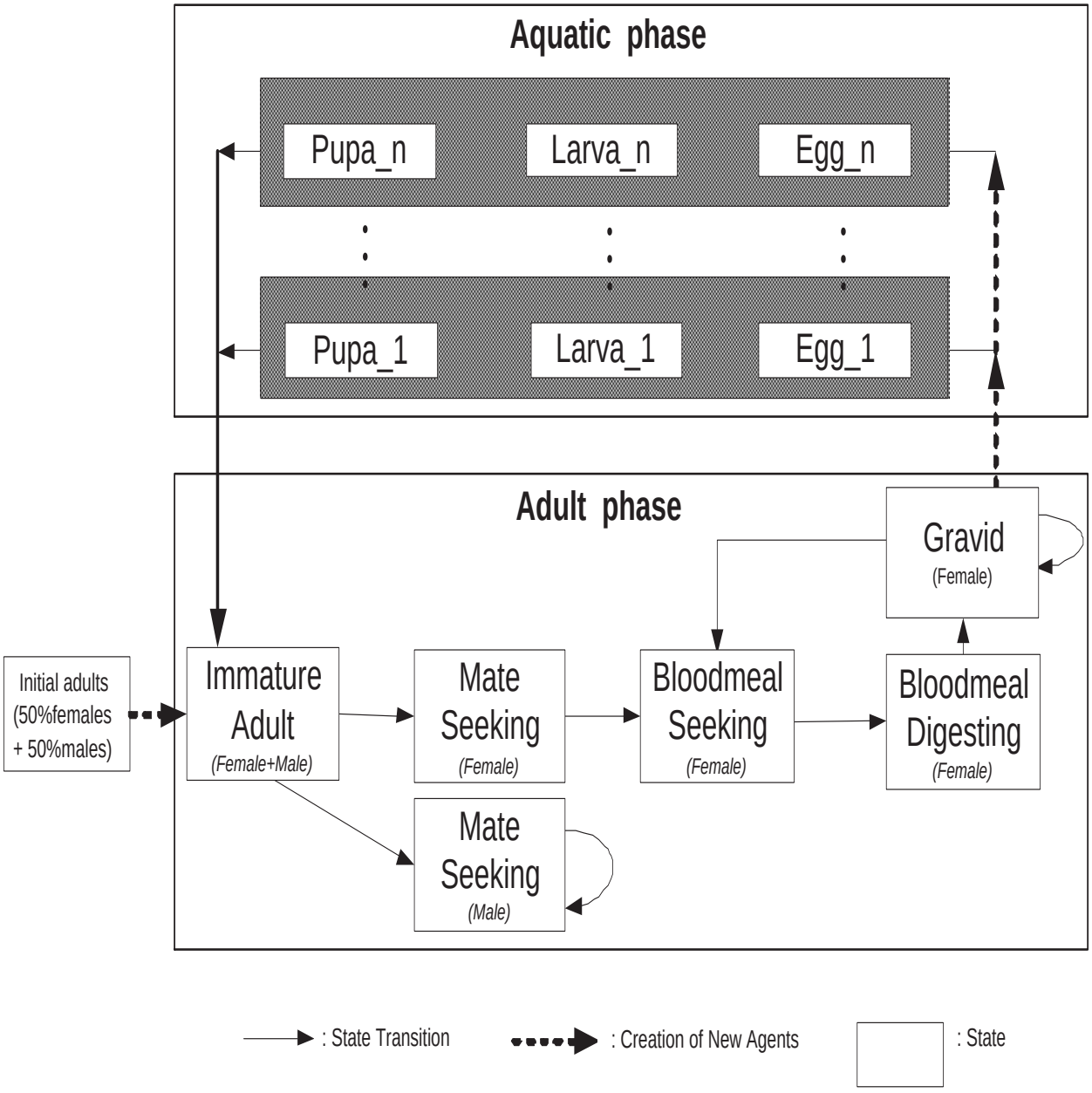


Figure 3.3. The Whole Biological Model of AGiLESim.

1. At ***IA***, a mosquito emerging from water has to wait a few days until its external skeleton hardens and it becomes dry. So when it emerges and the daily temperature is lower than 20℃, it usually takes up to 3 days. However, if the temperature is higher than 35℃, it only needs one day to grow up from an immature adult to a mature adult. Between 20℃ and 35℃, two days are needed before it locates a mate.

2. Coming out of ***IA***, male mosquitoes will stay at ***MS*** for their rest of life until they die. However, for female adults in our model, they can always successfully find males to mate with and enter ***BMS***, going out to search blood meals. We assume this state transition from ***MS*** to ***BMS*** is independent of the daily temperature.

3. At ***BMS***, females generally fly out and seek a host at night. We assume here that a female mosquito can always encounter and feed on at least one host on a given night. Once the female has completed biting the host, she will immediately search for a resting place to digest the meal. So the state transition to ***BMD*** is assumed to happen within one day and does also not depend on the daily temperature.

4. However, ***BMD*** is highly temperature-dependent. At this stage, mosquitoes at different daily temperatures take different lengths of time to digest meals and develop their eggs. When the temperature drops to 18℃, she needs to wait 4 days before she becomes gravid. But as long as the temperature slightly ascends to 23℃, the development time can be shorten to 2 days. Between 18℃ and 23℃, three days are needed.

5. At ***G***, one female mosquito can lay a clutch of around 80 eggs, which is

normally distributed with mean of 80 and standard deviation of 12. We arbitrarily set that a female only randomly samples at most 3 habitats each day. If all eggs are laid within one day, she will head back for ***BMS*** based on rule 6. If they are not, she has to stay at ***G*** and waits for another day to lay the rest of eggs. She does not leave ***G*** for ***BMS*** until she has no eggs left.

6. After oviposition, the time for a female to go back to search another meal, namely to return to ***BMS***, depends on how many habitats the gravid female has sampled on the previous night. When a female is able to find an unsaturated habitat and lay all developed eggs into that oviposition site, she will be able to move back to ***BMS*** on the same day. However, if she has to sample two habitats before she lays all eggs, the time to return to ***BMS*** is either 0 or 1 day, with a discrete probability distribution of 0.5 and 0.5 respectively. She has to wait for the next day to search another host if she lays its eggs among three habitats on the previous night.

The duration lengths (in days) of 5 adult states: ***IA***, ***MS***, ***BMS***, ***BMD*** and ***G*** are summarized in Table 3.1.

### 3.3.3 Scales Addressed in AGiLESim

We adopted discrete time step, the length of which is one day.

The simulation started with an initial population of 1000 adult mosquitoes: half females and half males at ***IA***. It was run on the machine with two dual-core Intel Xeon 3 GHz and eight 4GB DDR2 FB-DIMMs with Mac OS X Server 10.6.2. The simulation took around 40 minutes to get one-year data with the

| State | Duration (in Days) | | | |
|---|---|---|---|---|
| $ImmatureAdult$ | Temperature(℃) | $\leq 20$ | 21∼35 | $\geq 36$ |
| | Days | 3 | 2 | 1 |
| $MateSeeking$ | Temperature(℃) | -$\infty \sim +\infty$ | | |
| | Days | 0 | | |
| $BloodmealSeeking$ | Temperature(℃) | -$\infty \sim +\infty$ | | |
| | Days | 0 | | |
| $BloodmealDigesting$ | Temperature(℃) | $\leq 18$ | 19∼22 | $\geq 23$ |
| | Days | 4 | 3 | 2 |
| $Gravid(EggsRemaining)$ | Temperature(℃) | -$\infty \sim +\infty$ | | |
| | Days | $1 \sim +\infty$ | | |
| $Gravid(NoEggsRemaining)$ | Sample # of habitats/oviposition | 1 | 2 | 3 |
| | Days | 0 | 50%:0 50%:1 | 1 |

TABLE 3.1

The State Duration (in Days) Table.

daily average values of 7000 adult mosquitoes and 70,000 immature mosquitoes including eggs, larvae and pupae in the system. Although this machine has four cores, our simulation is currently not parallel. So in fact only one core was fully used when the simulation was running on the machine. The time will be much shorten after we introduce MPI into our simulation in the future.

## 3.4 Design Concepts

### 3.4.1 Interactions

The concept of interaction in an agent-based simulation refers to how agents communicate with, or affect other agents[28]. In order to resemble the real ecological system in which *Anopheles Gambiae* mosquitoes live, we assume that there

are three types of interactions in our model.

1. An interaction between a female adult and a male adult when they are mating.

   When a female adult enters ***MS*** stage, she will randomly choose one male adult also at ***MS*** to mate. After mating, the genotype of the selected male adult will be stored in one data field named as *MMaleGenotype* within the female agent. The genotypes of their offspring are based on it and the female's genotype. This is a so-called direct interaction[28], by which an explicit encounter among agents for information exchange has happened.

2. An interaction between an ovipositing female adult and a habitat.

   Some researchers in [37][38] has denoted that female adults of *Anopheles Gambiae* prefer to avoid ovipositing in conspecific larvae crowded habitats so that the impact of intra-specific competition and overcrowding on this species is avoided. In addition, eggs and pupae need to take up some space within one habitat, so these two populations also do affect the number of eggs one female will lay into that habitat. This interaction was implemented by a function that calculates how many eggs a gravid female can lay in a specific habitat (please see 3.5.3.3 about the function for more details). In this function, there are three arguments that are the egg, larva and pupa populations. This is also a direct interaction between a mosquito agent and a habitat agent.

3. An interaction between a gravid female adult and the aquatic agents in a habitat.

This interaction is actually implicitly expressed in the above second interaction. Whether gravid females lay eggs in one specific habitat or not is based on the cumulative or average influence of the aquatic residents living in that habitat. This kind of interaction is called as Field Interaction in [28]. In other words, each agent is affected by a local field of interaction that is created by other agents.

4. Different larvae within the same habitat compete for food and room.

   Since the survival of *Anopheles* larvae is affected by the quantity of food available and the size of space where larvae live [29], the shortage of food and limitation in space significantly increase mortality of larvae. Moreover, some research results demonstrated in [30] show that cannibalism and predation from older *Anopheles* larvae on younger *Anopheles* larvae are very common. So in our model, this interaction among larvae was implemented by assigning different daily mortality rates to different age groups of larvae. Since the older larvae are, the stronger and higher competition for food and living space they have. So older larvae have lower daily mortality rate than younger ones. The larval mortality function will be discussed in detail in 3.5.3.1.

   This competitive interaction is defined as a mediated interaction in [28], which means the individuals affect others by consuming common resources.

### 3.4.2 Stochasticity

We incorporate random numbers and probabilities into our simulation as follows:

1. Stochasticity is used to represent variability in weather data input.

We assume the daily temperature is normally distributed with mean of the monthly average temperature and standard deviation of 0.1. For example, if the monthly average temperature of one area in January we are modeling is 25℃, then the time series of daily temperatures in January will be obtained by drawing a value from $N(25, 0.1)$. But the temperature fluctuation within one day (24 hours) is neglected in our model.

One alternative to synthesizing the stochastic weather input is to incorporate a time series of observed real weather data. In order to include more natural weather trends, periodic and rare events, we might substitute the current stochastic weather model with real weather data collected in local weather stations in the future.

2. Specifying the statistical normal distribution for the state variables of mosquito agents.

   - After mating, one gravid female can lay a clutch of up to 120 eggs, which is drawn randomly from a normal distribution with an empirically determined mean of 80 and standard deviation of 12:

   $$Egg/clutch \sim N(80, 12)$$

   .

   - The cumulative development time at the larval stage: CDT_Larva, described in detail in 3.5.3.2. When CDT_Larva is greater than $1 + N(0, 0.1)$, the larval stage is considered completed:

   $$CDT\_Larva \sim 1 + N(0, 0.1)$$

- if an ovipositing female needs to sample two habitats to lay all eggs, the time for her to return to ***BMS*** is either 0 or 1 day, with a discrete probability distribution of 0.5 and 0.5 respectively.

3. Whether mosquito agents die or not at each time step is determined stochastically. This rule is used in the following four scenarios.

    - In each age group of adults, mosquito agents have the same probability to be dead. So here, we use a discrete uniform distribution to obtain a series of mosquitoes that need to be killed on a given day.
    - For the egg group in a habitat, we also use a discrete uniform distribution to choose a calculated number of eggs to kill.
    - The same discrete uniform distribution function is also used for the daily loss for each larval age group in each habitat.
    - For the pupa group in a habitat, the same discrete uniform distribution function is also used.

All stochastic numbers are generated by the third-part free computing routines provided by the GNU Scientific Library (GSL)[59].

### 3.4.3 Scheduling

In our model, time is treated as discrete, with processes happening over daily time steps. Ideally, during each time step, events should be concurrent, all happening simultaneously. For example, the daily updates of aquatic mosquitoes in each habitat and mature mosquitoes occur concurrently in the real world. But when we actually implement the simulation, we have to decide on the order in which all concurrent processes in our model are executed. Different executing

order will bring on different simulation data because the outcome of the previous event might influence the simulation of the next event. Therefore, we choose a predetermined order in which our events are executed.

There are totally five events happening in each time step, which are:

- Killing part adults based on adult daily mortality rates;
- Killing part aquatic mosquitoes in each habitat based on daily mortality rates;
- Updating aquatic mosquitoes in all habitats that survived during this time step;
- Updating adult mosquitoes that survived in this time step;
- Collecting the data for statistical analysis and biological observation. The data includes the population size of mosquitoes at each state and so on.

Our scheduling of specifying the exact order in which the above five events occur is shown in Fig. 3.4. We arbitrarily set a rule here that new emerging mosquito adults produced in Model3 and new born mosquito eggs created in Model4 do not be processed including killing and updating during the current time step. They have to wait for the next day.

### 3.4.4 Sensing

Sensing is the way that agents obtain knowledge about their world. In AG-iLESim, we assume that female adults are able to know how full a habitat is of aquatic mosquitoes. This assumption can be supported by several studies in [37][38].

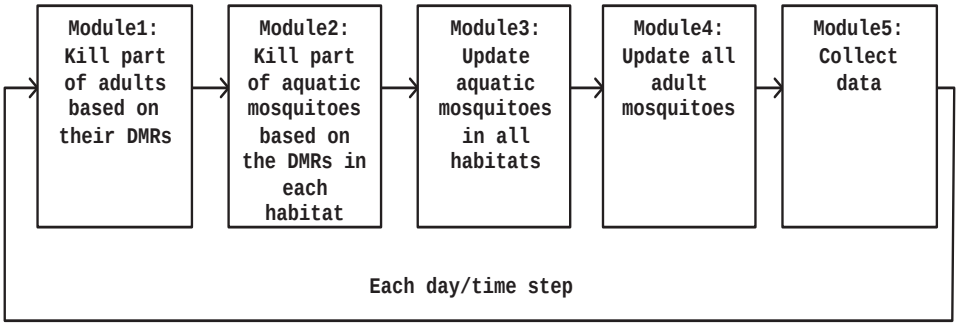


Figure 3.4. The scheduling Order of Five Events During Each Time Step in AGiLESim.

## 3.5 Details

### 3.5.1 Initialization

There are three kinds of input data needed to initialize our simulation. (The following are examples we have used for testing, verification and validation purposes.)

1. We start the simulation with a simple scenario: an arbitrary number of adult mosquito agents at ***IA*** with half females and half males are injected into the system. Since the initial population size has little impact on the population dynamics when the system reaches equilibrium, 500 adult females and 500 adult males are thought enough to warm up the whole system.

2. There are five habitats with the carrying capacities of 5,000, 5,000, 10,000, 20,000 and 30,000. The natural hazard mortalities of these habitats are the same, which are 0.1.

3. The precipitation parameter and the temperature profile. At present, the precipitation parameter used in DMR_larva is 1. The annual temperature

profile is generated stochastically, in which the daily temperature is normally distributed with mean of the average temperature of the corresponding month and standard deviation of 0.1.

### 3.5.2 Assumptions

1. Each batch of eggs a female adult lays consists of half females and half males.
2. Only the physiological hazard of aging affects the survival rate of adult females and males. No other natural hazards from the environment do contribution. Temperature is only one key factor affecting larval survival. In the real world, there are many other key factors such as water quality, predator, pathogens and so on [48, 49, 50].
3. When female mosquitoes enter ***BMS***, they can always find blood meals for the development of their eggs successfully.
4. Geographic properties of habitats have not been taken into consideration.
5. Ovipositing female adults can always successfully find breeding site(s) to lay their eggs on a given night.
6. After sampling three habitats, if the gravid female still has some mature eggs left on a given night, she will not search for breeding sites any more but find a place to rest and wait for another night.

### 3.5.3 Methods

#### 3.5.3.1 Daily Mortality Rates

1. Eggs and pupae:

Since mosquito eggs and pupae do not feed, no food competition happens at these two stages. Their daily mortality rates of DMR_egg and DMR_pupa are fixed at 0.1, which is a minimum daily mortality rate reflecting the effect of natural hazards on them.

$$DMR\_egg = DMR\_pupa = 0.1$$

2. Larvae:

In our model, larvae in different age groups have different daily mortality rates. According to the studies in [29], if larvae of *Anopheles Gambiae* live in an environment that is short of food and has limited space for their development, the mortality of these larvae will be significantly increased. Moreover, some research results demonstrated in [30] show that cannibalism and predation from older *Anopheles* larvae on younger ones are very common when there is no enough food on a habitat. In other words, older larvae have higher competition. Based on this observation, in our model, older larvae have lower daily mortalities than younger ones.

So the dail mortality rate of larvae in an age=$i$ (days) larval group is defined as follows:

$$DMR\_larva(x = i) = \alpha \cdot e^{\frac{1}{x \cdot K \cdot r}(\sum_{j=1}^{\infty} j \cdot N_j)} \tag{3.5.1}$$

where $\alpha$ is the basic mortality caused by natural hazards and we arbitrarily set it as 0.1; $K$ is the carrying capacity of the habitat where this group of larvae lives; $r$ is the precipitation coefficient; $\sum_{j=1}^{\infty} j \cdot N_j$ is one-day old larval equivalent effective index, where $j$ is the age (in days) of larvaes in this larval group, and $N_j$ is the abundance of larvae in this group.

3. Adults:

In the early 1950's, Macdonald firstly proposed that the survival rate of adult mosquitoes does not change as they grow older [44]. And this conclusion was widely accepted by a few researchers afterwards [19, 45, 46, 47]. They used the constant daily mortality rates in their models of mosquito population dynamics.

On the contrary, many investigators [40, 42, 43] indicated that adult mosquitoes do senesce and mortality is highly age dependent in adult females and males. [41] mentioned the mortality pattern can be formulated by the Gompertz mortality function (the logarithm of the mortality is linearly proportional to age). Later, researchers in [40] found that Logistic or Logistic-Makeham hazard functions provide the best fit than the Gompertz's for mortality patterns of the female and male cohorts in their experiments.

In our model, we adopt the later opinion of age-dependent mortality, namely the daily mortality rate of adult mosquitoes increases with age of the individuals. We also choose the Logistic mortality function as follows for both adult females and adult males:

$$DMR\_adult = \frac{a \cdot e^{Age \cdot b}}{1 + \frac{a \cdot s}{b}(e^{Age \cdot b} - 1)} \tag{3.5.2}$$

Where $a$ is the daily minimum mortality rate and we set it as 0.1; $b$ is the exponential mortality that rises with $Age$; $s$ is the degree of mortality deceleration.

This function can be interpreted as the proportion of adult mosquitoes that fail to survive each day due to the physiological hazard of aging. It does not take the other hazards such as natural predators and diseases and so on into account.

| Stage | Development Time in Days | | | | |
|---|---|---|---|---|---|
| *Egg* | Temperature(℃) | $\leq 15$ | 16∼20 | 21∼35 | $\geq 35$ |
| | Days | 4 | 3 | 2 | 1 |
| *Pupa* | Temperature(℃) | $\leq 25$ | | $\geq 26$ | |
| | Days | 2 | | 1 | |

TABLE 3.2

The Development Time at the Egg and Pupa Stages.

#### 3.5.3.2 Development Time at Each Stage

1. Since mosquitoes are a cold blooded animal, the development time at the egg and pupa stages highly directly depends on the temperature. At the egg stage, with decreasing temperature, there is a general increase of the development time for eggs to hatch [52, 53]. In our model, eggs take four days to hatch when the temperature falls to 15℃ or lower. However, as the temperature goes up to 36℃, the mosquito egg incubation period is only one day long. For pupae, they must live in water for two days when the temperature is below 25℃. Otherwise, at least one day is needed for the pupa development.
   The development time at the egg and pupa stages is summarized in Table 3.2.

2. The development time at the larval stage:

   At the larval stage, temperature is also a decisive regulator of the larval development. In the late 1970s and early 1980s [33, 34], people have derived a temperature-dependent development function for poikilothermic organisms

based on an assumption that the reaction rate of a single enzyme determines the development of poikilotherm organisms. In [31], researchers well investigated and summarized this function, and provided the parameters of the function with reasonable values, with which the curve drawn by the function well fit published or estimated *Anopheles gambiae* immature stage development time data.

In our model, we adopted this function at the larval stage, which is the development rate per hour at temperature T(°K):

$$DevR\_larva(T) = \frac{\rho_{25°C} \cdot \frac{T}{298} \cdot e^{[\frac{\Delta H_A^{\neq}}{R}(\frac{1}{298} - \frac{1}{T})]}}{1 + e^{[\frac{\Delta H_L}{R}(\frac{1}{T_{\frac{1}{2}L} - \frac{1}{T}})]} + e^{[\frac{\Delta H_H}{R}(\frac{1}{T_{\frac{1}{2}H} - \frac{1}{T}})]}} \tag{3.5.3}$$

The six parameters in the equation 3.5.3 are explained as follows [40]:

- $\rho_{25°C}$ : the development rate/hour when the temperature is at 25℃.
- $\Delta H_A^{\neq}$ : the enthalpy of activation of the reaction catalyzed by the enzyme (cal/mol).
- $\Delta H_L$: the enthalpy change associated with low temperature inactivation of the enzyme (cal/mol).
- $T_{\frac{1}{2}}L$: the temperature(°K) where 50% of the enzyme is inactivated by low temperature.
- $\Delta H_H$: the enthalpy change associated with high temperature inactivation of the enzyme (cal/mol).
- $T_{\frac{1}{2}}H$: the temperature(°K) where 50% of the enzyme is inactivated by high temperature.
- $R$: is the universal gas constant of 1.987(cal/mol).

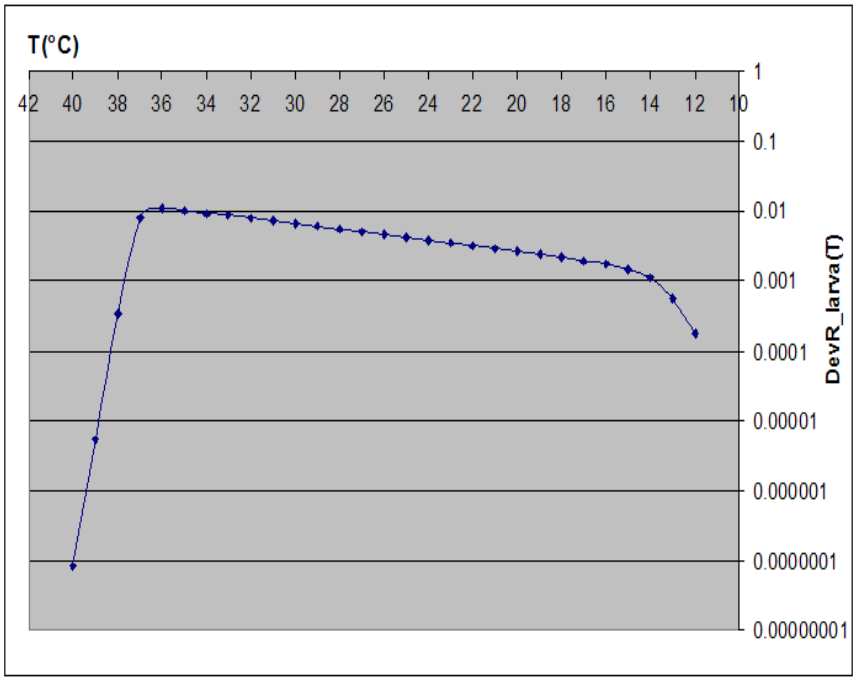


Figure 3.5. The DevR_larva curve Used in AGiLESim.

In our model, we use $\rho_{25^\circ C}$=0.00415, $\Delta H_A^{\neq}$ =15684, $\Delta H_L$=-229902, $T_{\frac{1}{2}}L$=286.4, $\Delta H_H$=822285, $T_{\frac{1}{2}}H$=310.3, and $R$=1.987 . Based on this set of parameter values, the numbers of DevR_larva(T) are plotted on a logarithmic scale against temperature on a linear scale in Fig 3.5:

We assume that temperature within 24 hours is constant. So the daily development rate of larvae is DevR_larva($T_i$)·24, where $T_i$ is the daily temperature on the $i^{th}$ day. Then the cumulative development time of larvae is:

$$CDT\_larva = \sum_{i=1}^{x} DevR\_larva(T_i) \cdot 24 \tag{3.5.4}$$

the larval stage is considered completed and immature mosquitoes enter the

pupa stage, when $CDT\_larva$ becomes greater than $1 + N(0, 0.1)$:

$$CDT\_larva > 1 + N(0, 0.1) \tag{3.5.5}$$

where $N$ is a normal distribution random variable. $N(0, 0.1)$ helps introduce mosquito variability into the larval stage. According to this inequality, we can calculate the value of $x$ , which is the total development time in days for a larva.

We can choose three typical temperatures from Fig 3.5 to preliminarily validate our choice of parameter values used in Equ 3.5.3. The three points respectively are 36℃, 26℃ and 16℃. The validation is conducted as follows: let us assume the daily temperature is fixed at 36℃ each day, then $DevR\_larva(36)$ based on Equ 3.5.3 can be calculated, which is 0.011113704. So the cumulative development time on a day with temperature of 36℃ - $CDT\_larva$ is $0.011113704 * 24 = 0.266728896$. Assuming the mosquito variability can be omitted here, based on Equ 3.5.5, the number of days for the larval development when temperature is constant at 36℃ is $\lceil 1/0.266728896 \rceil = 4(days)$. When the daily temperature is 26℃ or 14℃, the whole calculation is similar with that of 36℃. The development time of larvae at 26℃ or 16℃ is 10 days or 24 days. There is no significant difference between the three calculated estimates and the mean survival time lengths of *Anopehles gambiae* larvae raised in the laboratory [51]. Their experiment results are respectively 6.9, 13.5 and 25.5 in days .

3. The development time at the five adult stages:

   Please see Table 3.1.

#### 3.5.3.3 Oviposition Rule

Since most *Anopheles* mosquitoes are crepuscular (active at dusk or dawn) or nocturnal (active at night) [60], and they can fly for 1 to 4 hours continuously at up to 1-2km/h [62], we assume that a gravid female is able to sample at most 3 habitats on a given day. If she still has some eggs left after sampling three oviposition sites, she has to wait for another day to repeat the same sampling process to lay the remaining eggs. As long as she does not lay all developed eggs during this gonotrophic cycle, the process will continue until she dies.

The research results in [35, 36, 37, 38] show that high density of conspecific larvae present in one habitat deters oviposition of gravid *Anopheles* females in that particular habitat so that the impact from intra-specific competition and overcrowding on this species is avoided. In addition, eggs and pupae need to take up some space within one habitat, so these two populations also do affect the number of eggs one female will lay into that habitat.

On the basis of these observations, we assign a behavior to gravid female agents that when an ovipositing female randomly samples one habitat, she will determine if this habitat is already overcrowded or not, and how many eggs she will lay in it based on the equation 3.5.6:

$$O\_potential(i) = O_{max} \cdot (1 - \frac{\sum_{j=1}^{\infty} j \cdot N_j + N_{egg} + N_{pupa}}{K \cdot i}) \tag{3.5.6}$$

where $O_{max}$ is the number of eggs a female develops during one gonotrophic cycle that is drawn from a normal probability distribution with mean of 80 and standard deviation of 12. $i$ is the sampling coefficient, which is based on an observation that after a female adult has sampled at least one habitat on a given

night, she usually becomes not the same "picky" as before, and prefers to lay already well-developed eggs as much as she can into the following found habitats. $K$ is the carrying capacity of the sampled habitat. $\sum_{j=1}^{\infty} j \cdot N_j$ is the one-day old larval equivalent effective index that describes the effect of the whole larval population in different larval age groups and explicitly presents an idea that older larvae have higher impact on food and space competition than younger ones that live in the same habitat. $N_{egg}$ is the egg effective index that is the population size of eggs. $N_{pupa}$ is the pupa effective index that is the number of pupae. Both $N_{egg}$ and $N_{pupa}$ actually reflect the idea adopted in our model that no food competition happens during these two stages and their impact on other aquatic mosquitoes is from the space taken up by them.

#### 3.5.3.4 C++ Implementation of AGiLESim

The model is implemented in C++. There are five C++ files in all, which are AGiLESim.cpp, Mosquito.cpp, Mosquito.h, Habiatat.cpp and Habitat.h. You can download these files by:

svn co *https://anosim.svn.sourceforge.net/svnroot/anosim/cpp*

The biological model of AGiLESim shown in Fig 3.3 is interpreted as a state-transition flow on which the main simulation program of AGiLESim.cpp works. Fig 3.6 illustrates a simple example that how AGiLESim.cpp processes the whole course that a female mosquito egg grows up to a mature mosquito, and finally lays her very first clutch of eggs. In this example, we assume daily temperature is fixed at 25℃ and this mosquito lives long enough to finish her very first oviposition. In sum, at 25℃, egg, larva and pupa stages respectively take 2, 10 and 2 days. We can get these three values from the section 3.5.3.2. When the mosquito grows up

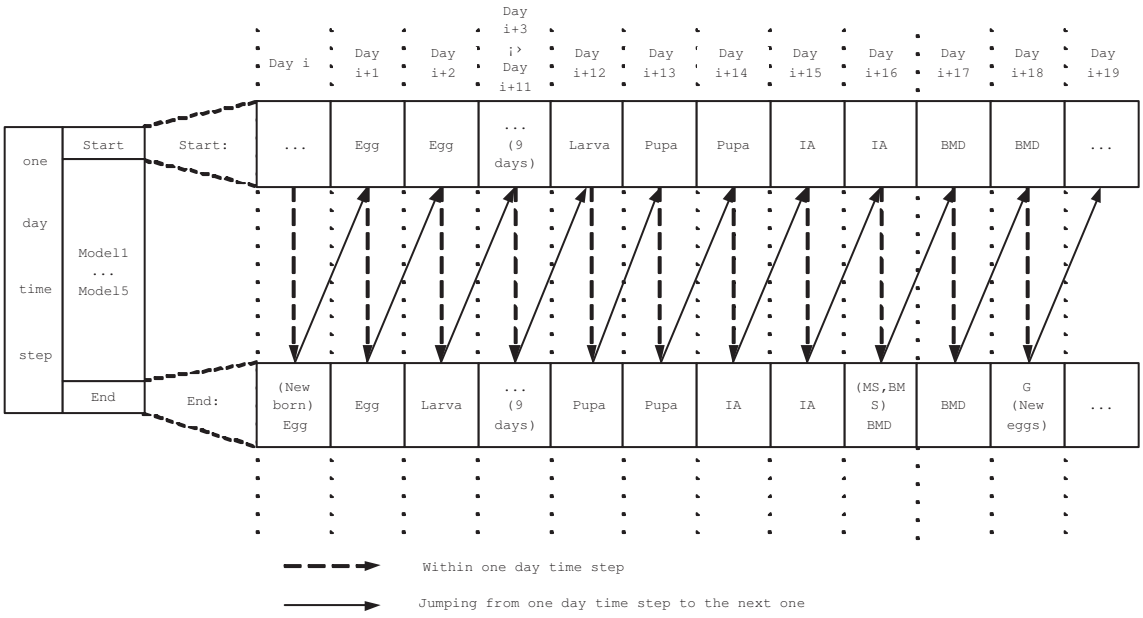


Figure 3.6. A State Transition Flow When the Daily Temperature is Fixed at 25℃.

to an adult, ***IA***, ***MS***, ***BMS***, ***BMD*** and ***G*** stages respectively need 2, 0, 0, 2 and 0 days. The data can be obtained easily from Fig 3.3.

The programming flow chart of the main simulation program of AGiLESim.cpp is shown in Fig 3.7.

Fig 3.8 shows the overview of all modules and the data flows we are using in this C++ simulation. There are six modules in AGiLESim that are processed in the following order: simulation initialization, killing part adults based on daily mortality rates, killing part immature mosquitoes in each habitat based on daily mortality rates, updating the state of adults, updating the state of aquatic mosquitoes and collecting data. The first model is only called once. However the later five modules are processed within each day or each time step.

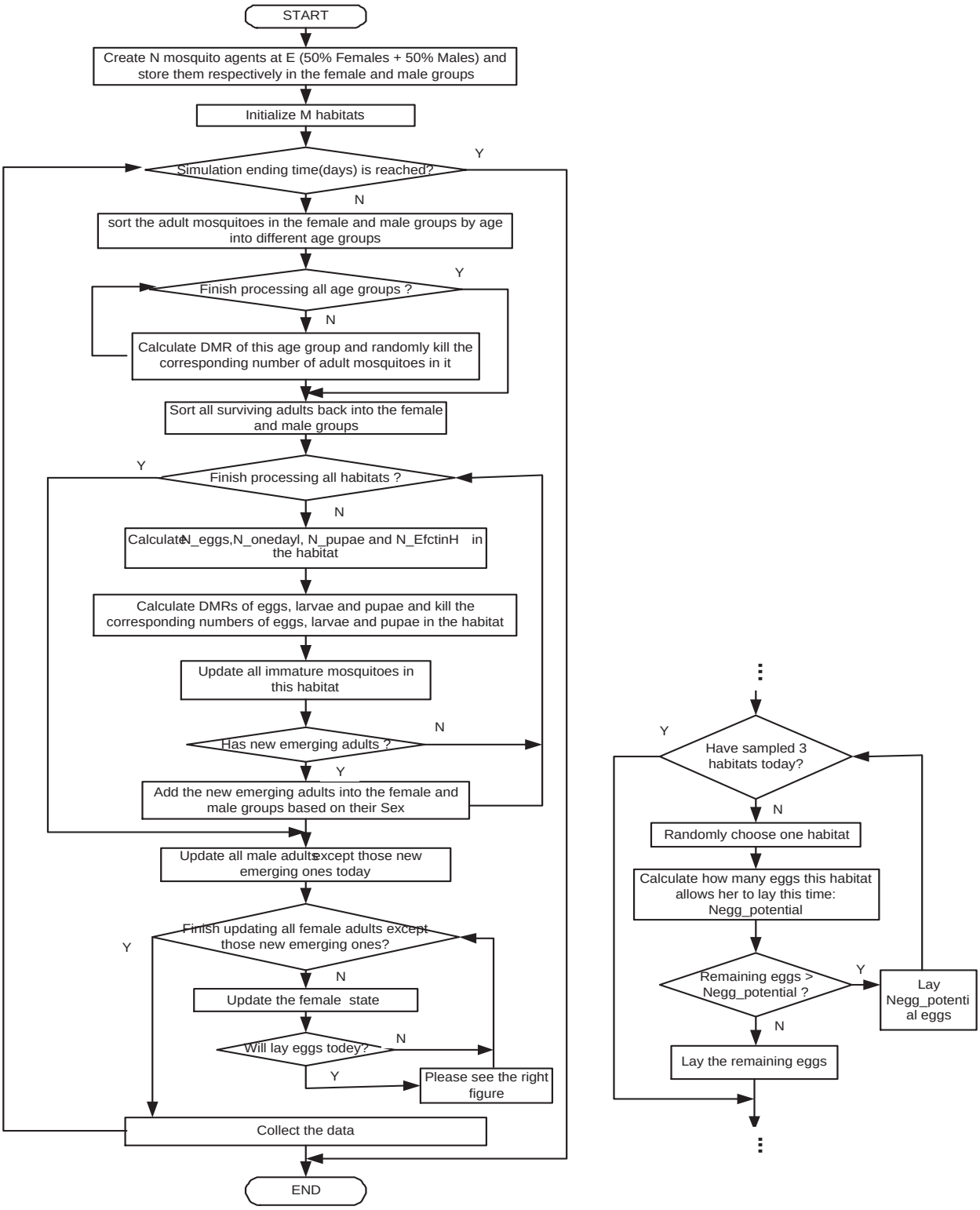


Figure 3.7. The Flowchart of the C++ Simulation of AGiLESim.

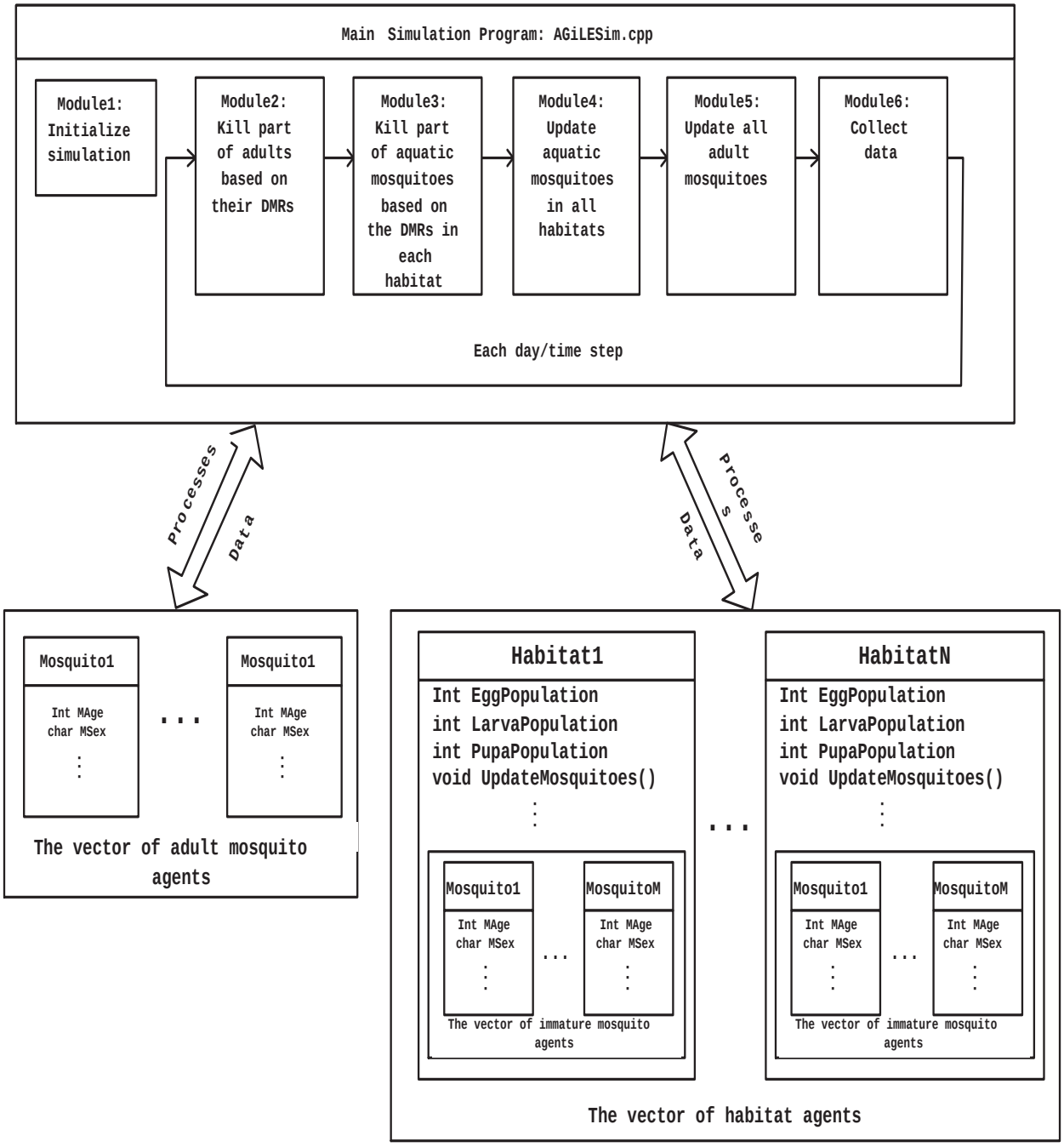


Figure 3.8. The Models and Data Flows in AGiLESim.

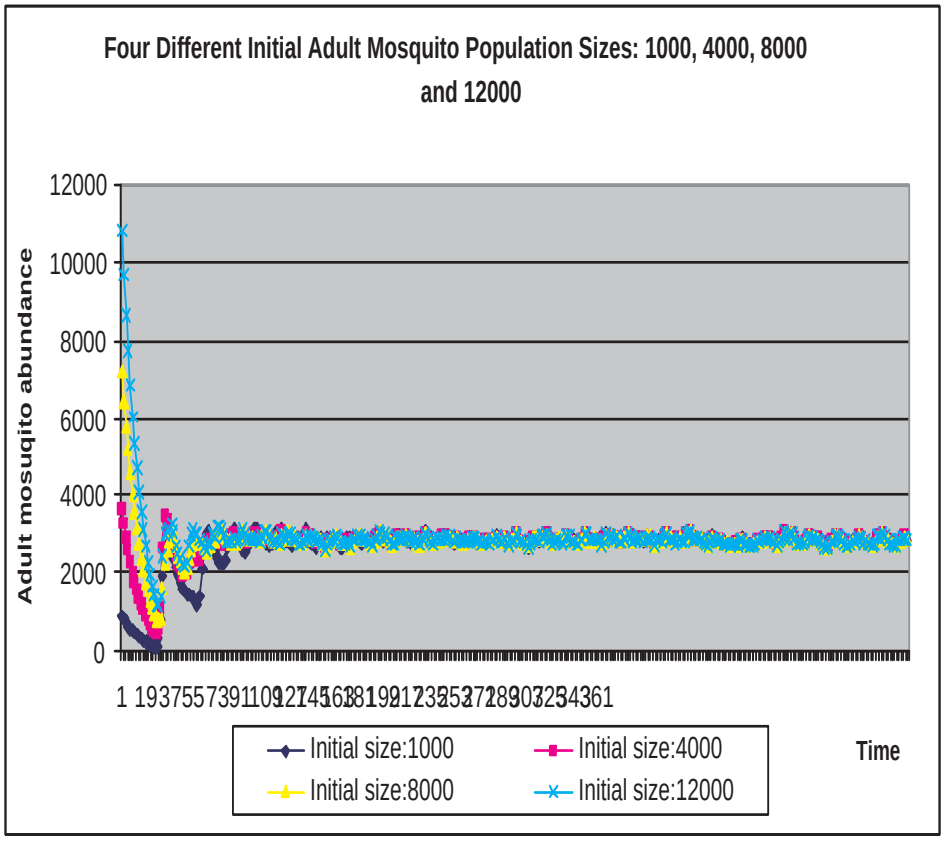


Figure 3.9. The Mosquito Abundances in the Four Simulations with Four Different Initial Adult Mosquito Populations.

## 3.6 Preliminary Results

### 3.6.1 The Initial Adult Mosquito Abundance

When the system is in equilibrium, the mosquito abundance is independent of the initial number of adult mosquitoes injected into the system. In Fig 3.9, we can see that whatever the initial numbers are: 1000, 4000, 8000, or 12000, the mosquito abundance in the four simulations finally oscillate around the same area when other conditions are the same.

### 3.6.2 Pseudo-random Number Generator Seeds

In our C++ simulation, we use a famous pseudo-random number generator called MT19937. It is a variant of the twisted generalized feedback shift-register algorithm, and is brought forward by Makoto Matsumoto and Takuji Nishimura and known as the "Mersenne Twister" generator [63]. As we all know, the same pseudo-random number generator with different seeds can generate different pseudo-random series. Therefore, we can get different sets of simulation data if we specify different seeds in our simulation.

How much impact brought by different pseudo-random seeds on simulation outputs will be? In order to answer this question, we run the C++ simulation 10 times with 10 different seeds, and plot ten curves of the female adult abundance in Fig 3.10. From this figure, we can conclude that varying pseudo-random seeds has little effect on the mosquito population.

### 3.6.3 The Proportion of Female Adults Older than 12 Days

When malaria parasites are ingested by a female mosquito adult, they usually take 10 up to 21 days to develop within the mosquito. This development of malaria parasites involves a series of steps: gametocytes ingested by *Anopheles* mosquitoes develop into zygotes, ookinetes, oocysts and finally sporozoites [64]. When sporozoites are found in a mosquito, then this mosquito is ready for malaria transmission to the next human host. This extrinsic incubation period at 27℃ was found to be 12 days [54, 55]. The duration of the extrinsic incubation period is an critical component of vectorial capacity that represents the malaria transmission potential of a mosquito population [65]. In addition, the longer an infected female mosquito survives, the more likely she survives the extrinsic incubation period

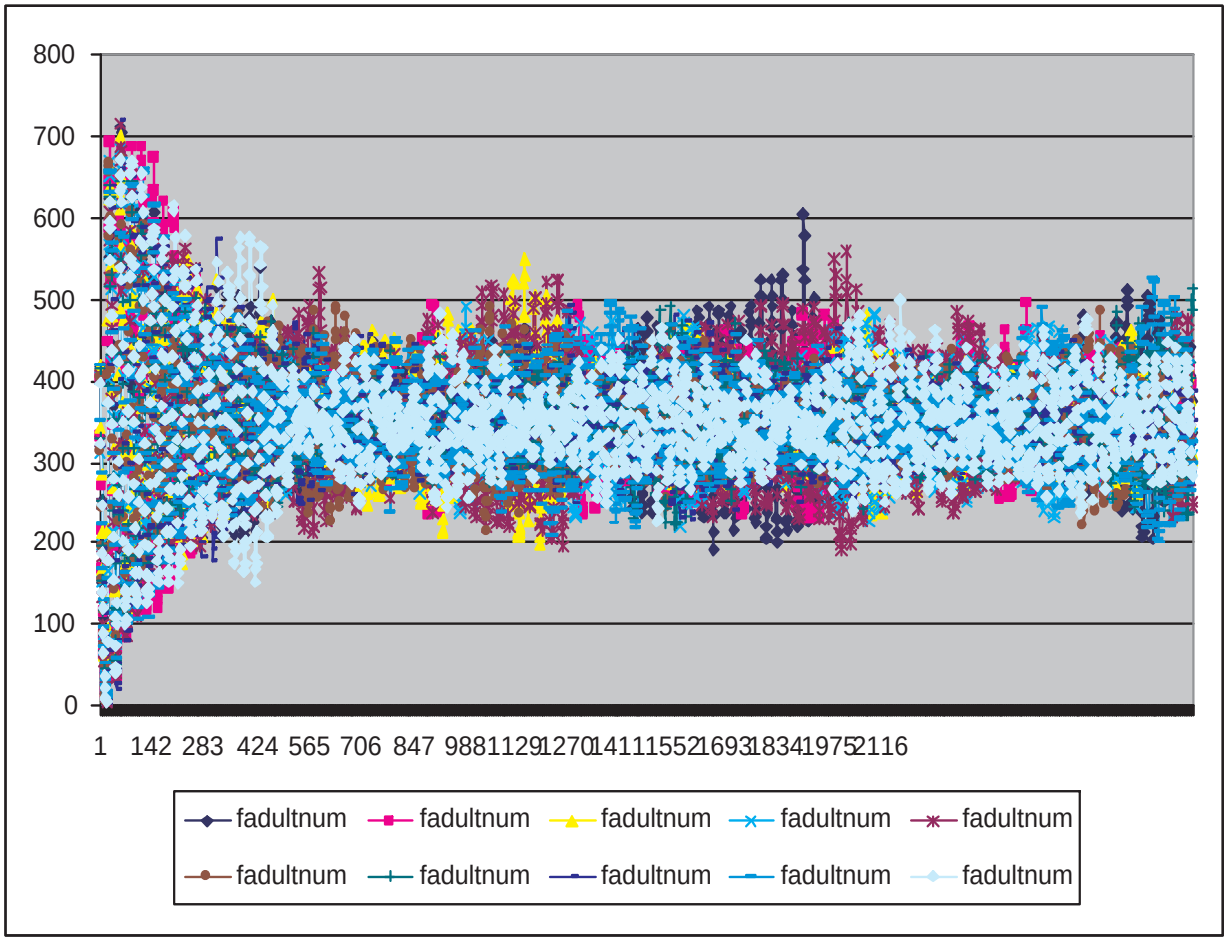


Figure 3.10. The Mosquito Abundances in the 10 Simulations with 10 Different Seeds.

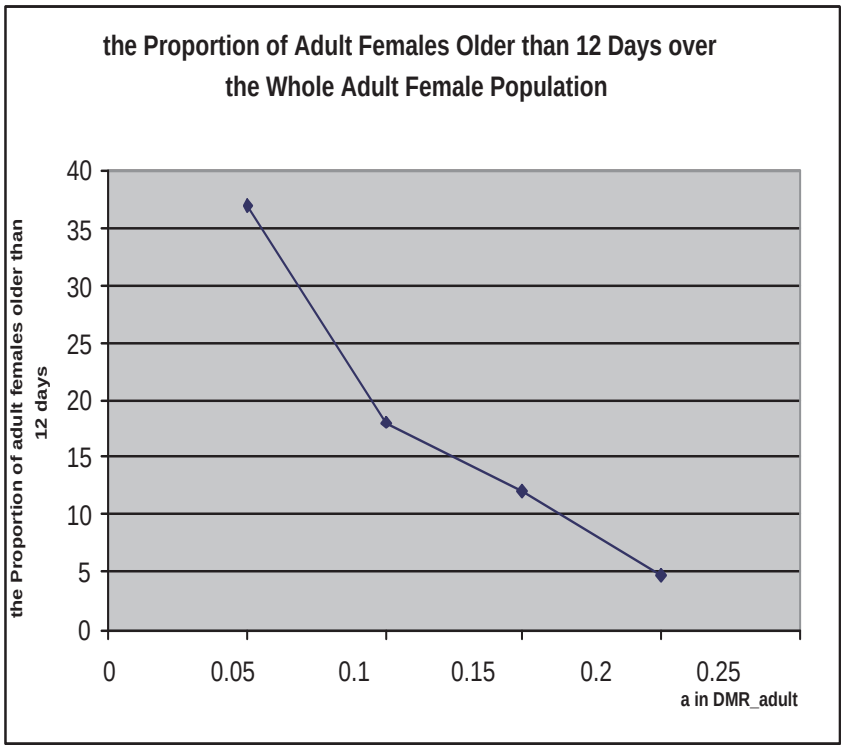


Figure 3.11. The Proportion Change of Adult Females Older than 12 Days with Different 'a' Values in DMR_adult.

and transmits the malaria disease to its next hunted human host.

Based on the above biologic observations, we investigate the proportion of female adults older than 12 days in our model. We find the main regulator of the proportion of adult females older than 12 days over the whole adult female population is the parameter-$a$ in $DMR_{adult}$ (please see Egu 3.5.2). From Fig 3.11, we can see that when we increase the value of $a$ from 0.05 to 0.2, the ration of female adults older than 12 days is reduced remarkably from around 37% to around 4%.

### 3.6.4 The Three Parameters in $DMR_{adult}$

The function of $DMR_{adult}$ is as follows, and it has been described in detail in 3.5.3.1. Here, we want to present the sensitivity analysis for the three parameters: a, b and s in $DMR_{adult}$.

$$DMR\_adult = \frac{a \cdot e^{Age \cdot b}}{1 + \frac{a \cdot s}{b}(e^{Age \cdot b} - 1)}$$

- $a$ (the daily minimum mortality rate): in Fig 3.12, we can see that as $a$ is deceased from 0.2 down to 0.05 and other conditions are kept the same, the adult mosquito population increases around 3 times when the system is in equilibrium, which means $a$ does have impact on the mosquito abundance. However, we find $a$ has much bigger effect on the older adult mosquitos than the younger ones. From Fig 3.13, we observe that the number of mosquitoes older than 12 days is increased to around 20 times. In other words, the system that has smaller $a$ in $DMR_{adult}$ has much more older mosquitoes than that having a slightly larger $a$.

- $b$ (the exponential mortality): we lessen $b$ from 0.05 to 0.04 and then to 0.03, the whole adult population slightly increases shown in Fig 3.14, and has no distinct change when the system reaches equilibrium. Compared to the impact of $a$, $b$ affects the mosquito abundance little. In Fig 3.15, as $b$ decreases from 0.05 to 0.03, the age>=12 days adult population raises around 40%.

- $s$ (the degree of mortality deceleration): similar to $b$, $s$ has also smaller effect than $a$ on both the mosquito abundance and the population with age>=12 days. In Fig 3.16, we find that as $s$ rises from 0.05 up to 0.2, the number of

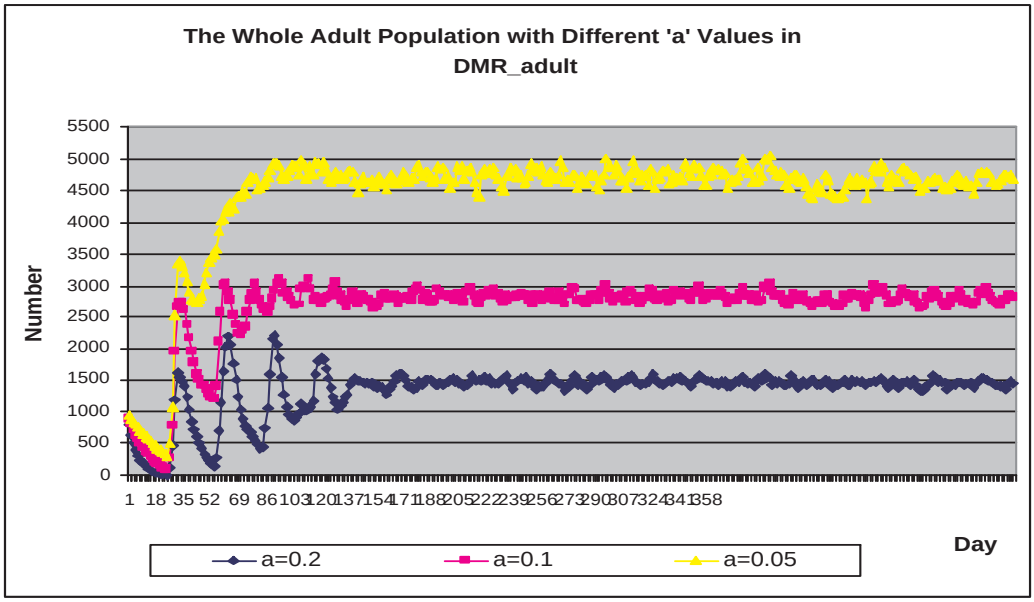


Figure 3.12. The Whole Adult Population with Different 'a' Values in DMR_adult.

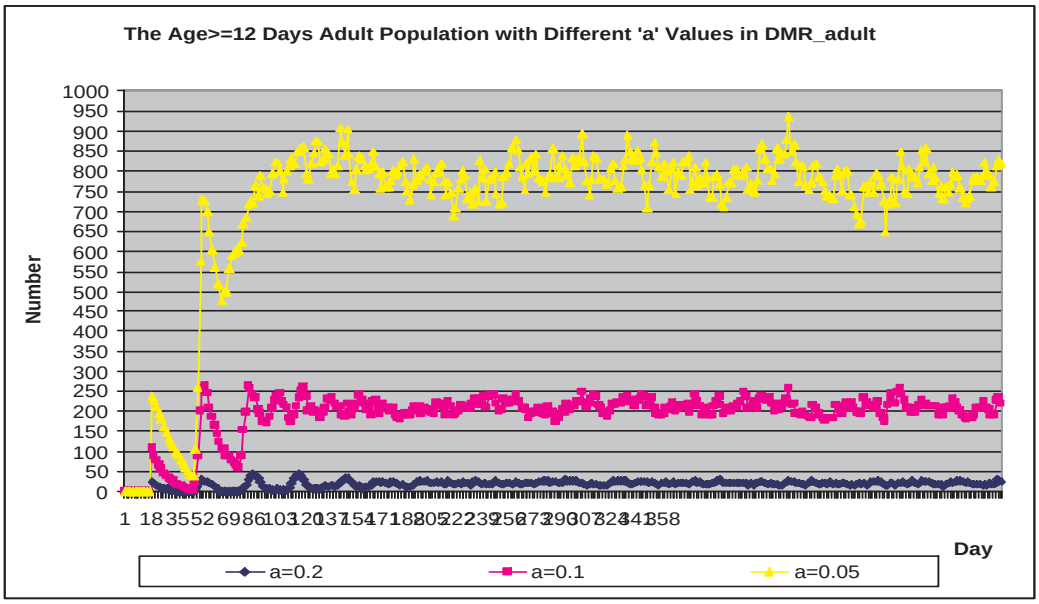


Figure 3.13. The Age>=12 Days Adult Population with Different 'a' Values in DMR_adult.

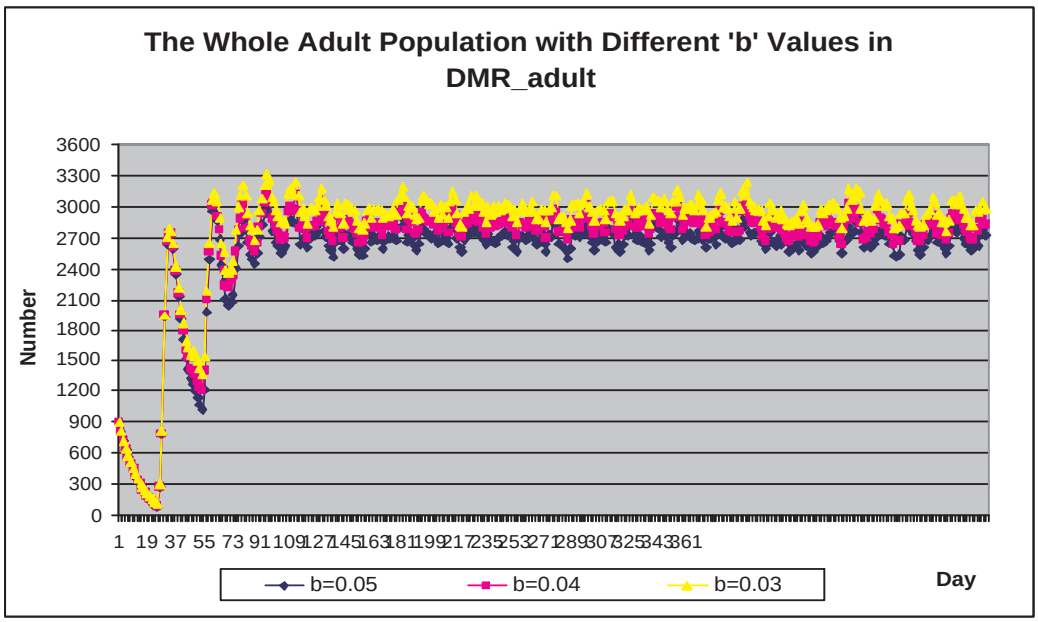


Figure 3.14. The Whole Adult Population with Different 'b' Values in DMR_adult.

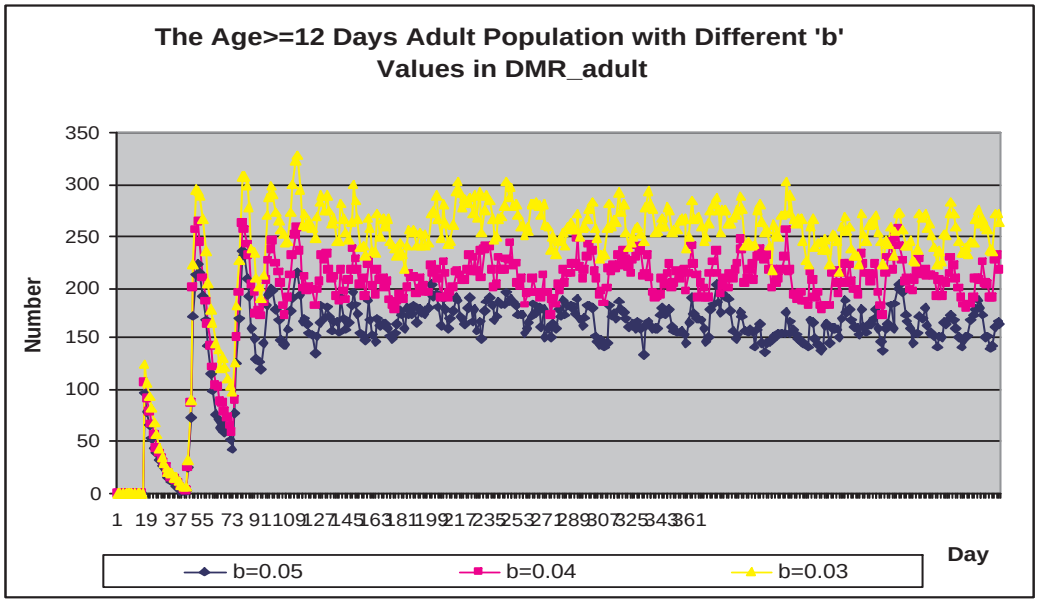


Figure 3.15. The Age>=12 Days Adult Population with Different 'b' Values in DMR_adult.

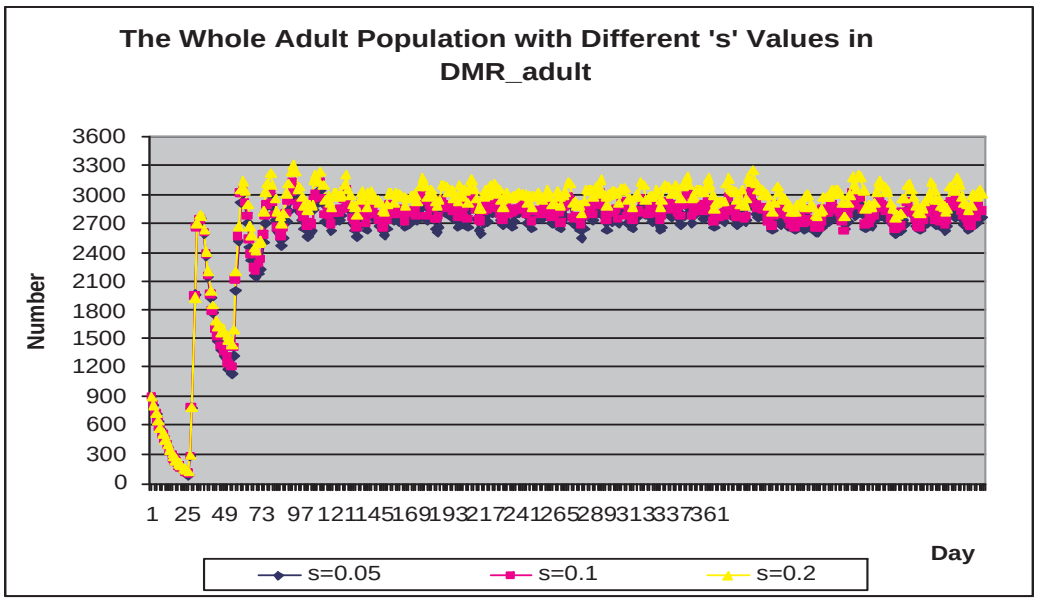


Figure 3.16. The Whole Adult Population with Different 's' Values in DMR_adult.

mosquitoes increases a little when the system becomes stable. The growth is only about 10%. For the older mosquito adults, the influence from $s$ is also small, and the increase of the number of older than 12 days mosquitoes is around 30% shown in Fig 3.17.

## 3.7 Conclusion

This chapter has presented our biological model of the *Anopheles gambiae* mosquito life cycle and its C++ simulation. In this simulation, we treat female and male mosquitoes at the aquatic and adult stages individually. Eight different states during a female mosquito life have been explored in detail. In addition, our model has captured the commonly observed proportion of female adults older than 12 days over the whole mosquito population. The dominant factor that controls

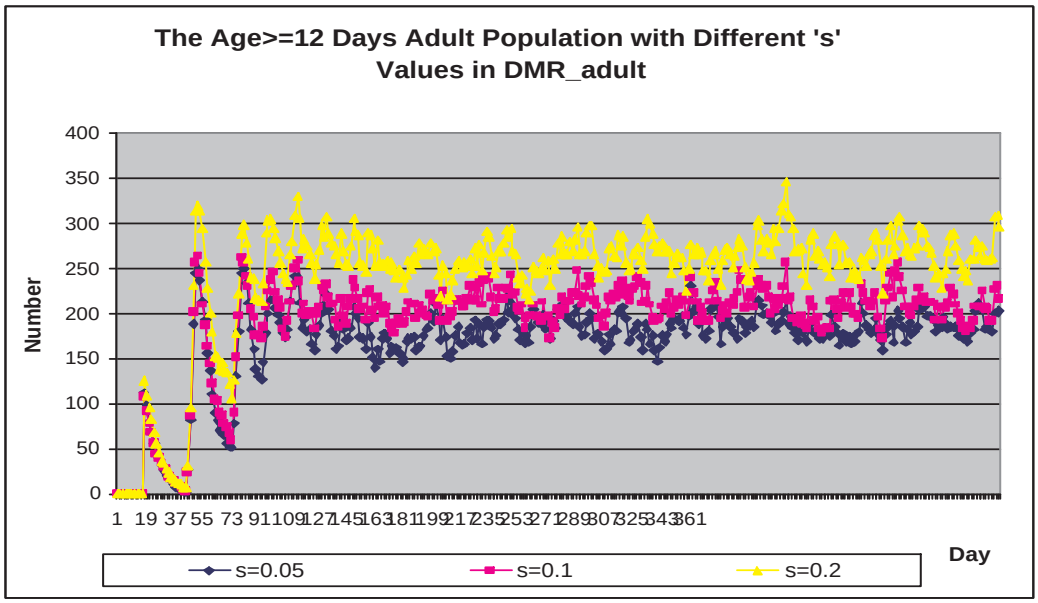


Figure 3.17. The Age>=12 Days Adult Population with Different 's' Values in DMR_adult.

this proportion has also been discussed here. The model takes into account the impact from one of environment factors-daily temperature on the mosquito state transition by increasing or decreasing some specific state durations. Finally, the preliminary sensitivity analysis for the five parameters used in this simulation and four preliminary results are represented in this part.

# BIBLIOGRAPHY


[1] Fletcher LA, Erickson DJ, Toomey TL, Wagenaar AC Handheld computers: a feasible alternative to paper forms for field data collection. *Eval Rev*, 27:165-178, 2003

[2] Jodi L. Vanden Eng, Adam Wolkon, Anatoly S. Frolov, Dianne J. Terlouw, M. James Eliades, Kodjo Morgah, Vincent Takpa, Aboudou Dare, Yao K. Sodahlon, Yao Doumanou, William A. Hawley, and Allen W. Hightower Use of handheld computers with global positioning systems for probability sampling and data entry in household surveys *Am J Trop Med Hyg.*, 77(2):393-399, 2007

[3] Softkeys Control Panel Applet v1.4 http://www.dotfred.net/SoftkeyAppletEx.htm

[4] Sprite Clone http://www.spritesoftware.com/products/spriteclone

[5] Peter Byass, Sennen Hounton, Moctar Oué draogo, Henri Somé, Ibrahima Diallo, Edward Fottrell, Axel Emmelin1 and Nicolas Meda Direct data capture using hand-held computers in rural Burkina Faso: experiences, benefits and lessons learnt *Tropical Medicine and International Health.*, 13:25-30, 2008

[6] Mobile Database Software-Visual CE http://www.syware.com/visualce.php

[7] Amy H. Auchincloss and Ana V. Diez Roux A new tool for epidemiology: the usefulness of dynamic-agent models in understanding place effects on health. *Am J Epidemiol*, 168(1):1C8, 2008.

[8] McKenzie, F. E., Wong, R. C. and Bossert, W. H. Discrete-event simulation models of Plasmodium falciparum malaria. *Simulation*, 71, 250-261, 1998.

[9] Gu W, Killeen GF, Mbogo CM, Regens JL, Githure JI, Beier JC Multi-agent systems in epidemiology: a first step for computational biology in the studey of vector-borne disease transmission. In *BMC Bioinformatics*, vol. 9, p.435, 2008.

[10] Weidong Gu, Gerry F. Killeen, Charies M. Mbogo, James L. Regens, John I. Githure and John C. Beier An individual-based model of *Plasmodium falciparum* malaria transmission on the coast of Kenya. In *Trans R Soc Trop Med Hyg*, 97:43-50, 2003.

[11] Jeffrey D. Sachs A new global effort to control malaria. *Nature*, 415, 680, 2002.

[12] Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI The global distribution of clinical episodes of Plasmodium falciparum malaria. *Nature*, 434 (7030): 214-7, 2005

[13] Malaria Facts http://www.cdc.gov/malaria/facts.htm. *Centers for Disease Control and Prevention.*

[14] Gollin, Douglas and Christian Zimmermann Malaria: Disease impacts and long-run income differences. *Manuscript: Department of Economics, University ofConnecticut*, 2007

[15] Overview of the MIS Documentation http://www.searo.who.int/EN/Section10 /Section21/Section1365_11100.htm *World Health Organization*, 2005

[16] Malaria Transmission Consortium (MTC) - Project Management Web Site http://neuron2.cc.nd.edu/mtc/index.php/Main_Page *Bill & Melinda Gates Foundation*, 2007

[17] R.Ross The prevention of malaria, 2nd ed. Murry, London, 1911.

[18] G. Macdonald The epidemilogy and control of malaria. *Oxford University Press*, London, 1957

[19] Dietz, K., Molineaux, L. and Thomas, A A malaria model tested in the African savannah. *Bulletin of the World Health Organization 50*, 347-357, 1974

[20] Aron, J. L. Mathematical modeling of immunity to malaria. *Mathematical Biosciences*, 90, 385C396, 1988

[21] Struchiner, C. J., Halloran, M. E. and Spielman, A. Modeling malaria vaccines. I: New uses for old ideas. *Mathematical Biosciences*, 94, 87C113, 1989

[22] McKenzie, F. E. and Bossert, W. H. An integrated model of Plasmodium falciparum dynamics. *Journal of Theoretical Biology*, 232, 411C426, 2005

[23] Smith T, Maire N, Ross A, Penny M, Chitnis N Towards a comprehensive simulation model of malaria epidemiology and control. *Parasitol*, 2008.

[24] Nakul Chitnisa, Thomas Smitha and Richard Steketeeb A mathematical model for the dynamics of malaria in mosquitoes feeding on a heterogeneous host population. *Journal of Biological Dynamics*, Vol.2, No.3: 259C285, 2008

[25] H. Van Dyke Parunak, Robert Savit and Rick L. Riolo Agent-based modeling vs. equation-based modeling: a case study and user's guide. *Proceedings of Workshop on Modeling Agent Based System (MABS98)*, Paris, 1998

[26] Charles M. Macal and Michael J. North Tutorial on agent-based modeling and simulation. *Proceedings of the 2005 Winter Simulation Conference*, 2005

[27] Charles M. Macal and Michael J. North Agent-based modeling and simulation:ABMS examples. *Proceedings of the 2008 Winter Simulation Conference*, 2008

[28] Volker Grimn and Steven F. Railsback Individual-based modeling and ecology. *Princeton University Press, 41 William Street, Princeton, New Jersey*, 2005

[29] Koenraadt CJM, Majambere S and Takken W The effects of food and space on the occurrence of cannibalism and predation among larvae of *Anopheles gambiae s.l. Entomologia Experimentalis et Applicata*, 112: 125-134, 2004

[30] Koenraadt CJM and Takken W Cannibalism and predation among larvae of the Anopheles gambiae complex. *Medical and Veterinary Entomology*, 17: 61-66, 2003

[31] Depinay JM, Mbogo CM, Killeen G, Knols B, Beier J, Carlson J,Dushoff J, Billingsley P, Mwambi H, Githure J, Toure AM, McKenzie FE A simulation model of African *Anopheles* ecology and population dynamics for the analysis of malaria transmission. *Malar J*, 3: 29, 2004

[32] Ikemoto, T. Intrinsic optimum temperature for development of insects and mites. In *Environmental Entomology*, 34(6): 1377-1387, 2005.

[33] R.M. Schoolfield, P.J.H Sharpe and C.E. Magnuson. Non-linear regression of biological temperature-dependent rate models based on absolute reaction-rate theory. In *J.theor.Biol*, 88:719-731, 1981.

[34] Peter J. H. Sharpe and Don W. DeMichele. Reaction kinetics of poikilotherm development. In *Theoretical Biology*, 4:649-670, 1977.

[35] Mccrae, A. W. Oviposition by African malaria vector mosquitoes. I. Temporal activity patterns of caged, wild-caught, freshwater Anopheles gambiae Giles sensu lato. *Ann. Trop. Med. Parasitol*, 78:307-318, 1983.

[36] Munga, S., Minakawa, M., Zhosu, G., Barrack, J. O-O., Githeko, A. K., And Yan, G. Effects of larval competitors and predators on oviposition site selection of Anopheles gambiae Sensu Stricto. *J. Med. Entomol*, 43:221-224, 2006.

[37] Gimnig JE, Ombok M, Otieno S, Kaufman MG, Vulule JM, Walker ED. Density-dependent development of Anopheles gambiae (Diptera: Culicidae) larvae in artificial habitats. *J Med Entomol*, 39:162-72, 2002.

[38] Sumba LA, Ogbunugafor CB, Deng AL, Hassanali A. Regulation of oviposition in Anopheles gambiae s.s.: role of inter- and intra-specific signals. In *J Chem Ecol*, 34:1430-6, 2008.

[39] Grimm V, Berger U, Bastiansen F. A standard protocolfor describing individual-based and agent-based models. *Ecol Model*, 198:115-26, 2006.

[40] Styer, L. M., J. R. Carey, J-L. Wang, and T. W. Scott Mosquitoes do senesce: departure from the paradigm of constant mortality. *Am. J. Trop. Med. Hyg*, 76:2007a. 111-117, 2007.

[41] Gompertz, B. On the nature of the function expressive of the law of human mortality and on a new method of determining the value of life contingencies. *Trans. Philos. Soc*, 115:1925. 513-585, 1925.

[42] Kershaw WE, Chalmers TA, Lavoipierre MMJ. Studies on arthropod survival. I.-The pattern of mosquito survival in laboratory conditions. In *Ann Trop Med Parasitiol*, 48: 442-450, 1954.

[43] Clements AN and Paterson GD. The analysis of mortality and survival rates in wild populations of mosquitoes. In *PJ Appl Ecol*, 18:373-399 , 1981.

[44] Macdonald G. The analysis of the sporozoite rate. In *Tropical Disease Bulletin*, 49:569-585, 1952.

[45] Miller DR, Weidhaas DE and Hall RC. Parameter sensitivity in insect population modeling. In *J Theor Biol.*, 42(2):263-274, 1973.

[46] Miller DR, Weidhaas DE and Hall RC. Malaria vectorial capacity of a population of *Anopheles gambiae*. An exercise in epidemiology entomology. In *Bulletin of the World Health Organization.*, 40:531-545, 1969.

[47] Molineaux, L and Gramiccia, G. The Garki project. Research on the epidemiology and control of malaria in the Sudan Savanna of west Africa. In *World Health Organization.*, Geneva, 1980.

[48] Clements, A.N. The biology of mosquitoes: development, nutrition, and reproduction. In *Chapman and Hall.*, London, 1992.

[49] Wallace, J.R. and Merritt, R.W. Influence of microclimate, food and predation on *Anopheles quadrimaculatus* (Diptera:culicidae) growth and development rates, survivorship, and adult size in a Michigan pond. In *Environmental Entomology.*, 28:233-239, 1999.

[50] Koenraadt, C.J.M and Takken, W. Cannibalism and predation among larvae of the the *Anopheles gambiae* complex. In *Medical and Veterinary Entomology.*, 17:61-66, 2003.

[51] M.N. Bayoh and S.W. Lindsay. Temperature-related duration of aquatic stages the Afrotropical malaria vector mosquito *Anopheles gambiae* in the labortary. In *Medial and Veterinary Entomology.*, 18:174-179, 2004.

[52] Kettle DS and Sellick G. The duration of the egg stage in the races of Anopheles maculipennis Meigen (Diptera, Culicidae). In *J Anim Ecol.*, 16:38C43, 1947.

[53] Daniel E. Impoinvil, Gabriel A. Cardenas, John I. Gihture, Charles M. Mbogo, and John C. Beier. Constant temperature and time period effects on *Anopheles Gambiae* egg hatching. In *J Am Mosq Control Assoc.*, 23(2):124C130, 2007.

[54] Noden BH, Kent MD and Beier JC. The impact of variations in temperature on early *Plasmodium falciparum* development in Anopheles stephensi. *Parasitology*, 111:539-545, 1995.

[55] Gilles MT and Warrel DA. Bruce-Chwatt's essential malariology. *3rd ed. London: Edward Arnold*, 1993.

[56] Yaw A. Afrane, Tom J. Little, Bernard W. Lawson, Andrew K. Githeko, Guiyun Yan. Deforestation and vectorial capacity of *Anopheles gambiae* giles mosquitoes in malaria transmission, Kenya. *Emerg Infect Dis*, 14(10):1533-8, 2008.

[57] Ramanathan R. Intel Multi-Core Processors. http://www.intel.com/technology/architecture/downloads/quad-core-06.pdf, 2007.

[58] Michael Kanellos Faster, cheaper memory on the horizon. http://news.cnet.com/Faster-cheaper-memory-on-the-horizon/2100-1001_3-236256.html, 2007.

[59] GSL-GNU Scientific Library http://www.gnu.org/software/gsl/,2009 *Free Software Foundation.*

[60] *Anopheles* Mosquitoes http://www.cdc.gov/malaria/biology/mosquito/ *Centers for Disease Control and Prevention.*

[61] Biology http://www.cdc.gov/malaria/biology/index.htm *Centers for Disease Control and Prevention.*

[62] Kaufmann C and Briegel H Flight performance of the malaria vectors *Anopheles gambiae* and *Anopheles atroparvus*. *J. Vector Ecol*, 29(1):140-153, 2004.

[63] Makoto Matsumoto and Takuji Nishimura Mersenne twister: a 623-dimensionally equidistributed uniform pseudo-random number generator. *ACM Trans. Model. Comput. Simul.*, 8(1):3-30, 1998.

[64] Schema of the Life Cycle of Malaria http://www.cdc.gov/Malaria/biology/life_cycle.htm *Centers for Disease Control and Prevention.*

[65] Garrett-Jones C Prognosis for interruption of malaria transmission through assessment of the mosquito's vectorial capacity. *Nature*, 204:1173-1175, 1964.

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